

GW26-e4478**Effects of zinc status on high-fat diet-induced cardiac hypertrophy**Shudong Wang,^{1,†} Zhiguo Zhang,¹ Zheng Xu,¹ Yang Zheng[†]¹Cardiovascular Center of the First Hospital, the Jilin University

OBJECTIVES We investigated the effect of dietary zinc supplementation and deficiency in mice consuming a high-fat on cardiac inflammation, cardiac fibrosis, and left ventricular function and structure using an animal model of adolescent obesity.

METHODS Male C57BL/6J mice (3 weeks of age) were fed either high fat diet (HFD, 60% kcal fat) or normal diet (ND, 10% kcal fat) containing low zinc (L-Zn, 10 mg Zn per 4057 kcal), normal zinc (N-Zn, 30 mg Zn per 4057 kcal) or high zinc (H-Zn, 90 mg Zn per 4057 kcal) for 3 or 6 months. Left ventricular function and structure were measured by Echocardiography. TNF- α (TNF- α), nuclear factor kappa-B (NF- κ B), B-cell CLL/lymphoma 10 (BCL10), caspase recruitment domain (CARD9), and phosphorylated and total MAPK p38 were assessed by western blot. The mRNA expression of connective tissue growth factor (CTGF), transforming growth factor β 1 (TGF- β 1), and atrial natriuretic peptide (ANP) in the heart were quantified by RT-PCR. The cardiac collagen content was analyzed by Sirius red staining. For myocyte cross-sectional area, sections were stained for membranes with FITC-conjugated WGA (wheat germ agglutinin).

RESULTS We found that HFD increased the expression of both phosphorylated and total p38 MAPK in the heart, along with the increased heart weight and hypertrophy in a time-dependent manner. Echocardiography demonstrated the cardiac hypertrophy in HFD mice, which was confirmed by WGA staining at cellular level. Although echocardiography and WGA staining revealed signs of cardiac hypertrophy in all obese mice, the increase in left ventricular (LV) mass and diameter was significantly more pronounced in Zn-defect HFD mice, and the HFD with H-Zn attenuated the hypertrophy. Cardiac inflammatory levels and fibrosis were increased in obese animals compared to mice fed by ND. Cardiac hypertrophy increased level was positive correlation with inflammatory response and fibrosis change. The cardiac structural changes and cellular and molecular hypertrophy was significantly more pronounced in 6 months than 3 months. In 3-month time-point, Zn-defect HFD significantly increased the expression of TNF- α , BCL10, CARD9, ANP, CTGF, TGF- β 1 and NF- κ B slightly increased. In contrast, at 6-month time-point, Zn-defect HFD significantly elevated levels of NF- κ B, p38 MAPK, but only slightly increased TNF- α , BCL10, CARD9, ANP, CTGF, TGF- β 1. Zn-supplemented HFD reduced the gene activity above. No changed cardiac fibrosis and structure was noticed in ND disregarding Zn levels. HFD with L-Zn increased the BCL10/CARD9, resulted in NF- κ B nuclear translocation, and increased p38 MAPK gene activity. Inhibition of p38MAPK reduced the cardiac hypertrophy induced by HFD with Zn deficiency.

CONCLUSIONS Obesity with zinc deficiency elevated p38MAPK gene expression via BCL10/CARD9/NF- κ B pathway, and its effect is blocked by zinc supplementation, demonstrating the potential.

GW26-e4594**Late sodium current plays a role in proarrhythmic and antiarrhythmic effects of QT prolonging drugs of multichannel blocking properties**

Lu Ren, Lin Wu

Peking University First Hospital

OBJECTIVES Proarrhythmic and antiarrhythmic effects of QT prolonging drugs vary significantly. The purpose of this study was to examine the role of late sodium current as a modulator of proarrhythmic and antiarrhythmic effects of multichannel blocking drugs.

METHODS New-Zealand White rabbit hearts were isolated and perfused in Langendorff mode. Hearts were paced at a rate of 1 Hz after thymo-ablation of AV node. Monophasic action potential duration (MAPD) from the epicardium and ECG signals were recorded in normal hearts and in hearts pretreated with a late I_{Na} enhancer ATX-II before and after the exposure of increasing concentrations of dronedarone (1 nM-10 μ M), amiodarone (1 nM-10 μ M) and ranolazine (0.1-100 μ M) in a cumulative manner.

RESULTS ATX-II (1-3 nM) alone prolonged LV MAPD₉₀ by 189 \pm 3, 255 \pm 17, and 328 \pm 23 ms (n =5, P < 0.05) from control of 171 \pm 3 ms. Dron alone and Ran alone caused concentration-dependent "monotonic" prolongations of MAPD₉₀ by up to 6 \pm 1 ms and 60 \pm 4 ms (n=8, P < 0.05), causing no arrhythmias. Amio alone prolonged MAPD₉₀ by 2 \pm 2 ms at the concentration of 30 nM and shortened MAPD₉₀ by 13 \pm 6ms

(n =10, P < 0.05) at the concentration of 10 μ M, without causing any arrhythmias. However, in the presence of 3 nM ATX-II, a stepwise increase in the concentrations of Amio and Dron were associated with a biphasic response, initially inducing arrhythmic activity and then suppressing it. Dron and Amio significantly increased MAPD₉₀ by 35 \pm 3 ms (n =4, P < 0.05) and 41 \pm 2 ms (n=12, P < 0.05) at the concentration of 300 nM and 30 nM, but decreased MAPD₉₀ by 12 \pm 10 ms (n =4, P < 0.05) and 73 \pm 4 ms (n =12, P < 0.05) at the concentration of 10 μ M, respectively. When hearts were pretreated with 1 nM ATX-II, the prolongation of MAPD₉₀ by Ran was only 43 \pm 14 ms (n =6, P < 0.05), and when hearts were pretreated with 3 nM ATX-II, MAPD₉₀ was decreased by up to 107 \pm 10 ms (n =11, P < 0.05), no arrhythmias observed.

CONCLUSIONS When late I_{Na} is augmented, amiodarone and dronedarone have concentration - dependent biphasic effects to induce and then suppress arrhythmic activity owing to their proarrhythmic window, but ranolazine had no proarrhythmic window so that it caused no proarrhythmic activities.

GW26-e4602**Role of NRG-1 released from cardiac microvascular endothelial cells in ischemia/reperfusion myocardium and its mechanism of action**

Qimeng Hao, Wenyi Guo

Xijing hospital

OBJECTIVES To explore the effects of NRG-1 that released from CMECs on cardiomyocytes during ischemia/reperfusion injury and discuss the possible mechanism.

METHODS Cardiac myocytes were isolated from the hearts of neonatal rats and CMECs from the adult rats. CMECs - cardiomyocytes coculture model was established. Then cells were endured simulated I/R (4 h/4 h). Collected CMECs culture medium during SI/R. CMECs were randomly divided into two groups: Control group, SI/R group (ischemia 2, 4, 6h, reperfusion 4h). While cardiomyocytes were randomly divided into following groups: Control group, SI/R group, SI/R + Coculture group, SI/R + Coculture + anti-ErbB2 (ErbB2 inhibitor) group, SI/R + NRG-1 group, SI/R + NRG-1 + anti-ErbB2 group, SI/R + NRG-1 + PD group. The cell viability of cardiomyocytes was measured by MTT assay. The apoptosis of cardiomyocytes was detected by TUNEL method. The expression of secreted NRG-1 in CMECs culture medium, phosphorylation of ErbB2 and ERK and COX-2 in cardiac myocytes were analyzed by Western blot. Measured caspase-3 activity reflected the apoptosis of cardiomyocytes.

RESULTS The cardiomyocytes viability was impaired in the SI/R (4h/4h) group (P < 0.01 vs. Control) while increased in the SI/R + Coculture group (P < 0.05 vs. SI/R). Within the groups of CMECs, the secretion of NRG-1 was remarkable increased in the time of 4h/4h under SI/R (P < 0.01) when compared with the Control group. Within the groups of cardiomyocytes, the apoptosis index and Caspase-3 activity were increased after SI/R (27.97 \pm 0.90 vs. 3.58 \pm 0.23, P < 0.01; 375.93 \pm 11.76 vs. 100.00 \pm 0.00, P < 0.01). While trained with Coculture or NRG-1 during SI/R could reduce the apoptosis index and Caspase-3 activity (16.82 \pm 1.03 vs. 27.97 \pm 0.90, P < 0.01; 166.16 \pm 15.15 vs. 375.93 \pm 11.76, P < 0.01). Besides, they can significant up-regulate the level of phosphorylation of ErbB2 and ERK and the expression of COX-2 (P < 0.01 vs. Control and SI/R). However, when cardiomyocytes were pretreated with ErbB2 or ERK1/2 inhibitor, the effect of Coculture and NRG-1 vanished (P < 0.01).

CONCLUSIONS In the process of I/R, the secretion of NRG-1 in CMECs protect cardiomyocytes against ischemic reperfusion injury through up-regulation of pErbB2 and activation of downstream ERK/COX-2 signal.

GW26-e2426**A network pharmacological approach to the treatment of cardiovascular and cerebrovascular diseases of Naixintong capsule**

Xianghui Ma, Pan Li, Bin Lv, Xiaoqing Jiang, Ting Wang, Qian Zhou, Xiaoying Wang

Tianjin University of Traditional Chinese Medicine

OBJECTIVES Naixintong capsule (NXT) consists of 16 kinds of Chinese herbal medicines which mainly containing Radix Astragali, Radix Paeoniae Rubra, Radix et Rhizoma Salviae Miltiorrhizae, Radix Angelicae Sinensis, Rhizoma Chuanxiong, Flos Carthami, Radix Achyranthis Bidentatae, Pheretima Ramulus Mori and Ramulus